REMARKS

This amendment and these remarks are responsive to the Office action dated May 19, 2003. Claims 94-115 are pending in the application. In the Office action, the Examiner rejected claims 94-115 as being indefinite under 35 U.S.C. § 112 and/or obvious under 35 U.S.C. § 103(a). Applicants traverse these rejections. Applicants contend that the rejected claims are neither indefinite nor obvious. Nevertheless, to reduce the number of issues under consideration in this response, and to expedite the issuance of a patent, applicants have amended claim 94 and canceled claims 106 and 107. Moreover, applicants have presented arguments showing that the cited references teach away from the subject matter of applicants' claims, and that the subject matter of these claims provides unexpected benefits. Accordingly, applicants respectfully request reconsideration of the rejected claims, and prompt issuance of a notice of allowance.

Claim Rejections – 35 U.S.C. § 112

The Examiner rejected claims 94-115 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Applicants traverse these rejections. Applicants believe that the claims as filed are definite. Nevertheless, to reduce the number of issues under consideration, and to expedite the issuance of a patent, applicants have amended claim 94 and canceled claims 106 and 107.

A. Claim 94

The Examiner rejected claim 94 under 35 U.S.C. § 112, second paragraph, contending that the phrase "contacting the substrate or any product [of] the operation of the enzyme" is vague and confusing. The Examiner stated that (1) it is "unclear whether

applicant in this step contacts the *substrate* only, or alternatively it includes the *mixture* of the substrate with the enzyme," and (2) that th "types of enzymatic reaction" and "the associated products" are unclear. Applicants disagree. Nevertheless, to more particularly point and distinctly claim aspects of their invention, applicants have amended claim 94, without narrowing its scope, as follows:

> 94. (Amended) A method of detecting the activity of an enzyme that operates on a substrate to form a product in a sample, comprising:
> contacting the substrate with the enzyme **in the sample**;
> contacting the **sample** [~~substrate or any product produced by operation of the enzyme~~] with a binding partner that specifically binds to the substrate or to **a** [~~the~~] product **of the operation of the enzyme,** but not to both, wherein the binding partner includes gallium that is required for binding between the binding partner and the substrate or **the** product;
> detecting a response, based on luminescence polarization, indicative of the extent of binding between the substrate or the product and the binding partner without separating the bound substrate or product from the unbound substrate or product; and
> correlating the response with the activity of the enzyme.

The types of enzymatic reactions covered by this claim, and the associated enzymes, substrates, and products, are those that may be assayed using a binding partner that includes a gallium involved in specific binding between the binding partner and the substrate or the product of the reaction. These enzymatic reactions include but are not limited to kinase reactions, phosphatase reactions, phosphodiesterase reactions, and cyclase reactions, among others.

B. Claim 106

The Examiner rejected claim 106 under 35 U.S.C. § 112, second paragraph, contending that "macromolecule" is vague and indefinite. The Examiner stated that it is "unclear what 'macromolecule' applicant refers to." Applicants disagree. The word "macromolecule" is a term of art referring to a large molecule that would be readily

understood by a person of ordinary skill in th art. Nevertheless, to reduce the number of issues und r consideration, and to expedite the issuanc of a patent, applicants have canceled claim 106, without prejudice, reserving their right to pursue the claim in a subsequent continuation application.

C. Claim 107

The Examiner rejected claim 107 under 35 U.S.C. § 112, second paragraph, contending that "nanoparticle" is vague and indefinite. The Examiner stated that the "nanometer range" of the nanoparticle is unclear. Applicants disagree. The word "nanoparticle" is a term of art referring to a small particle that would be readily understood by a person of ordinary skill in the art. Nevertheless, to reduce the number of issues under consideration, and to expedite the issuance of a patent, applicants have canceled claim 107, without prejudice, reserving their right to pursue the claim in a subsequent continuation application.

Claim Rejections – 35 U.S.C. § 103

The Examiner rejected claims 94-101, 106-108, 110, and 112-115 under 35 U.S.C. § 103(a) as being unpatentable over Nikiforov (U.S. Patent No. 6,472,141) in view of Posewits et al. (Anal. Chem. 7:2883-92 (1999)). Applicants traverse these rejections.

The Examiner stated that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to replace the conventional metal ions of Fe3+, or Al3+ for capturing phosphopeptides as taught by Nikiforov with the Ga ion as taught by Posewitz et al. with a reasonable expectation of success." (Office action, page 4, first full paragraph.)

Applicants disagre , for at l ast two reasons.

First, applicants believe that Posewitz teaches away from r placing Fe(III) with Ga(III) in fluorescence polarization assays, because Posewitz implies that Ga(III) binds with phosphorylated peptides less avidly than Fe(III). Posewitz is directed to the use of immobilized metal affinity chromatography (IMAC) to purify phosphorylated peptides for mass spectrometry. This purification involves two steps: (1) retention, in which a metal retains a phosphorylated peptide, and (2) elution, in which the metal releases the phosphorylated peptide. Posewitz may argue that Ga(III) offers advantages over Fe(III) for purification. However, these advantages appear to arise because the phosphorylated peptides are more readily eluted (i.e., unbound) from Ga(III) columns than Fe(III) columns. For example, in Fig. 3 of Posewitz, phosphorylated peptides are at least tenfold better at unbinding from Ga(III) than Fe(III). In contrast, the methods recited in applicants' pending claims use binding (not unbinding) between Ga(III) and an enzyme substrate or product to detect enzyme activity. Thus, Posewitz teaches away from substituting Ga(III) for Fe(III) in polarization assays, because the unbinding associated with Ga(III)'s enhanced elution ability would be expected to reduce binding-related changes in polarization associated with enzyme activity.

Second, applicants have found an unexpected benefit to using Ga(III) instead of Fe(III) in fluorescence polarization assays. Specifically, metals are well-known fluorescence quenchers (i.e., extinguishers). Indeed, Pierce Biotechnology recently began selling a kinase assay system in which enzyme activity is observed using fluorescence quenching that accompanies interaction of a fluorescently labeled phosphorylated peptide with iron. However, applicants have discovered that Ga(III),

unlike F (III), does not appear significantly to quench fluorescence in th ir binding assays. (See, e.g., Application, page 33, lines 8 and 9.) This difference is particularly beneficial in polarization assays, because the net polarization of a mixture of bound and unbound luminophores will depend on the separate polarizations of the bound and unbound luminophores, weighted in part by their relative brightnesses. Therefore, quenched luminophores will contribute to the net polarization only minimally, if at all, because their luminescence emissions are quenched. Thus, the net polarization of a mixture in which bound luminophore is quenched will arise mostly or exclusively from unbound luminophore, making corresponding binding assays insensitive to the binding that they are supposed to detect. These shortcomings are consistent with applicants' observation that there do not appear to be any Fe(III)-based polarization assays. The Nikiforov patent does not disclose data in which a metal was used in a binding partner, nor to applicants' knowledge has Nikiforov published any papers showing such an assay. In contrast, applicants' application shows data for Ga(III)-based polarization assays. Moreover, applicants have developed a variety of commercial products that are now for sale for detecting the activity of over fifteen different enzymes using Ga(III)-based polarization assays. Applicants released the first of these products in May 2001.

In summary, without any suggestion or motivation in the prior art to combine and/or modify the cited references, and because the cited references actually teach away from their combination, the Examiner has failed to establish prima facie obviousness of the rejected claims. Moreover, even if the Examiner were to establish prima facie obviousness, it would be rebutted by the unexpected benefits and superior properties demonstrated by the claimed assay. Thus, for at least these reasons,

applicants respectfully request withdrawal of th r jections under 35 U.S.C. § 103(a) and prompt allowance of the p nding claims.

Applicants believe that they have addressed all of the issues raised by the Examiner in the Office action, and that the application currently is in condition for allowance. However, if they Examiner has any questions or comments, or if a telephone interview would advance the prosecution of the application, the Examiner is encouraged to call applicants' undersigned attorney at the address listed below.

CERTIFICATE OF FACSIMILE

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office, Attention: Examiner Changhwa J. Cheu, Group Art Unit 1641, to facsimile number: (703) 308-4556 on July 30, 2003.

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